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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/033,835	12/24/2001	Yunik Chang	HME/7679.012	9339

29085 7590 04/30/2004

HOWARD EISENBERG, ESQ.
2206 APPLEWOOD COURT
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EXAMINER	
MAIER, LEIGH C	

ART UNIT	PAPER NUMBER
1623	

DATE MAILED: 04/30/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/033,835	CHANG ET AL.	
	Examiner	Art Unit	
	Leigh C. Maier	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *04 February 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *24-90* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *24-90* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 5 February 2004 has been entered.

Claims 1-23 have been canceled. Claims 47 and 54 have been amended. Previously withdrawn claims 74-79 have been added. Newly submitted claims 82-90 have been added. Claims 24-90 are pending. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. Any objection or rejection not expressly repeated has been withdrawn.

Claim Rejections - 35 U.S.C. § 102

Claims 82, 85, and 87 are rejected under 35 U.S.C. 102(b) as being anticipated by KATA et al (Acta Pharm. Hung., 1984).

KATA discloses a stable aqueous solution comprising 2.25% β–CD and 1.5% metronidazole. See the English translation at page 11, 4th paragraph. The reference indicates that the composition is stable, but is silent with regard to the precise conditions recited in the claims. Since the Office does not have the facilities for preparing the claimed materials and comparing them with prior art inventions, the burden is on Applicant to show a novel or unobvious

difference between the claimed product and the product of the prior art. See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *In re Fitzgerald*, 619 F.2d 67, 205 USPQ 594 (CCPA 1980).

Claim Rejections - 35 U.S.C. § 103

Claims 24, 27-29, 31, 32, 40, 41, 43-58, 63, 65-68, 71-74, 76-87, 89, and 90 are rejected under 35 U.S.C. 103(a) as being obvious over KATA et al (Acta Pharm. Hung., 1984) and CHIEN et al (US 4,032,645).

The invention is as set forth in the previous Office action. Applicant has added new claims 74 and 76-79 drawn to a method for "increasing the enhancing effects of betacyclodextrin on the solubility of metronidazole . . . comprising combining niacin or niacinamide. . ." Upon further review, the examiner interprets this to be essentially the same method as recited in claim 71: a method for using less BCD to solubilize MTZ than would ordinarily be necessary by the addition of another solubilizing agent.

KATA teaches as set forth above. The composition has utility as an injection solution. The reference does not teach the use of other solubility-enhancing agent(s).

CHIEN teaches aqueous compositions comprising 5.0 to 6.5% metronidazole and a variety of solubility enhancing agents, such as niacinamide (Nd) and niacin (Nn) (1-5%, with 2% exemplified). See col 2, lines 16-53 and examples. This composition also has utility as an injection solution.

It would have been obvious to one having ordinary skill in the art at the time the invention was made to prepare an injection solution comprising MTZ of about 1% or greater and the solubility-enhancing agents β–CD and 1% or more of Nd and/or Nn by combining the

components in water. One of ordinary skill would be motivated to use a combination of solubility-enhancing agents for their additive effects. It would be within the scope of the artisan to select any of the solubility-enhancing agents taught by CHIEN. In the absence of unexpected results, it would be obvious to select either Nd *or* Nn in the absence of the other agent.

It would be expected that if the solubility-enhancing agent, β–CD, were used *in combination with* another solubility-enhancing agent, such as Nd, it would take less of the β–CD to solubilize the same amount of the agent that is to be solubilized because of the additive effect of multiple solubility-enhancing agents. It would be within the scope of the artisan to optimize the amounts of the various components with routine experimentation.

Regarding claims 29, 31, and 32, each composition is recited as a product-by-process. However, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process.

The kit claims differ from the composition claims only in the presence of a container. It would be obvious to prepare and/or store the composition taught by the combination of references in a container.

Applicant's arguments filed 5 February 2004 have been fully considered but they are not persuasive.

Applicant appears to argue that CHIEN teaches that Nn and Nd are solubility-enhancing agents only in the presence of ethanol. The examiner disagrees with this characterization. The reference teaches that a number of agents have solubility-enhancing properties. There is no

teaching that they must be used in tandem to have this utilty. It would be within the scope of the artisan to select any of these agents to combine with β–CD and MTZ to enhance the solubility of the latter.

Applicant further contends that there is no teaching (1) to use Nd without other agents; or (2) use Nd (with or without other agents) in combination with β–CD to increase the solubility of MTZ in water. However, the reference specifically teaches that Nn and Nd are each a "'hydrotropic agent' . . . an agent which forms a solubility-increasing complex," similar to a cyclodextrin. See col 2, lines 47-53. Again, it would be within the scope of the artisan to select any known solubility-enhancing agent. The artisan would be motivated to combine them for the additive effects. Even if, for the sake of argument, Applicant's interpretation of the reference were correct, the claims would not preclude the addition of ethanol or any other solubility-enhancing agent.

Claims 24, 26-68, 70-74, and 76-90 are rejected under 35 U.S.C. 103(a) as being obvious over KATA et al (Acta Pharm. Hung., 1984) and CHIEN et al (US 4,032,645) in view of CZERNIELEWSKI (US 5,849,776).

The invention is as set forth in the previous Office action.

KATA and CHIEN teach as set forth above. Both of the references are directed toward preparing metronidazole compositions with increased solubility. The references do not teach the preparation of a gel or the treatment of dermatological disorders, including rosacea.

CZERNIELEWSKI teaches the preparation of an aqueous gel comprising up to about 5% by weight of metronidazole for the treatment of dermatological disorders, including rosacea. See paragraph bridging col 1-2 and col 2; lines 42-44; and example 2.

It would have been obvious to one having ordinary skill in the art at the time the invention was made to prepare an aqueous solution comprising metronidazole of about 1% or greater and the solubility-enhancing agents β–CD and 1% or more of niacinamide and/or niacin as set forth above. It would be further obvious to add gelling agent(s) to prepare a gel for the treatment of dermatological disorders, including rosacea. One of ordinary skill would be motivated to prepare a gel using the solubilizing agents taught by KATA and CHIEN in order to prepare gels of higher concentration (>1%) of metronidazole because of the limited water solubility of this drug.

The additive effects of the components, product-by-process claims, kits, and the selection of any known solubility-enhancing agent have been addressed above.

Applicant's arguments filed 5 February 2004 have been fully considered but they are not persuasive. Applicant adds no additional arguments not addressed above.

Claim 24, 25, 27-29, 31, 32, 40, 41, 43-58, 63, 65-69, 71-87, 89, and 90 is rejected under 35 U.S.C. 103(a) as being obvious over KATA et al (Acta Pharm. Hung., 1984) and CHIEN et al (US 4,032,645) in view of LOFTSSON (US 5,324,718).

The invention is as set forth above. Dependents of the method of preparing the instant compositions require adding the metronidazole to the water after the other components have been added to the water.

KATA and CHIEN teach as set forth above. The references do not specifically exemplify a method of preparation comprising adding the metronidazole to the water after the other components have been added to the water.

LOFTSSON teaches the preparation of compositions comprising lipophilic and/or water labile drugs in combination with cyclodextrins and other solubilizing agents. See abstract. The reference further suggests the use of metronidazole. See col 7, lines 53-54. The reference specifically exemplifies a method of preparing such a composition by adding the drug to a water solution comprising the cyclodextrin and other solubilizing agents. See example 13.

It would have been obvious to one having ordinary skill in the art at the time the invention was made to prepare the compositions taught by KATA and CHIEN, comprising the step of adding the metronidazole to the water after the other components have been added, for the art-disclosed utility. One of ordinary skill would reasonably expect success in using this method because LOFTSSON had taught that this method is useful for preparing compositions comprising lipophilic drugs, cyclodextrins, and other solubilizing agents.

Applicant's arguments filed 5 February 2004 have been fully considered but they are not persuasive. Applicant contends that LOFTSSON discloses that the "increased drug solubility enhancement of the cyclodextrin/polymer combination is due to the formation of a complex involving the drug, the cyclodextrin, and the polymer" and that there is "no disclosure or suggestion in the prior art that betacyclodextrin and either niacinamide or niacin for [sic] such complexes." The examiner does not find this to be on point because the reference was used to teach the step of adding the MTZ to a solution after the other agents are dissolved in water.

However, as discussed above, the claims would not preclude the addition of a polymeric solubility-enhancement agent, such as those taught by LOFTSSON.

Purported Unexpected Results

Applicant argues that the present claims are patentable because the combination of BCD, and Nn or Nd produces unexpected advantageous properties pertaining to the aqueous solubility of MTZ and discusses the reasoning in points a.-e.

This reasoning is not found to be persuasive. Applicant is drawing a conclusion based on an implicit assumption that each solubilizing agent is acting of the full amount of MTZ, whereas in Applicant's example, it is known that for a 1.0% solution of MTZ, the amount of BCD present is enough to dissolve 80% of the MTZ present. There is only 0.2% "left over" in need of solubilization.

To illustrate, convert the MTZ to some arbitrary unit of measure. A solution comprising 0.5% BCD will dissolve 8 units of MTZ. A solution of 3% Nd will dissolve 10 units of MTZ, so a solution of 1% Nd should dissolve 3.3 units of MTZ. (In part e. of the argument, Applicant has assumed linearity, so the examiner will also.) Therefore, a solution comprising 0.5% BCD and 1% Nd would be expected to dissolve about 11 units. Converting back to percentages, one would expect this combination to provide about 1.1% MTZ, so the 1% solution is not surprising. A similar analysis would apply to the discussion of niacin.

It is applicant's position that 0.5% BCD is the minimum amount necessary to prepare a solution of 0.8% MTZ. One way to provide an apples-to-apples comparison would be to

determine the minimum amount (X%) of Nd to prepare an 0.8% MTZ. Then, if 0.5% BCD + X% Nd provides a >1.6% MTZ, synergy would be demonstrated.

Examiner's hours, phone & fax numbers

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leigh Maier whose telephone number is (571) 272-0656. The examiner can normally be reached on Tuesday, Wednesday, and Friday 7:00 to 3:30 (ET).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. James O. Wilson (571) 272-0661, may be contacted. The fax number for Group 1600, Art Unit 1623 is (703) 872-9306.

Visit the U.S. PTO's site on the World Wide Web at http://**www.uspto.gov**. This site contains lots of valuable information including the latest PTO fees, downloadable forms, basic search capabilities and much more.

Leigh C. Maier
Patent Examiner
April 29, 2004